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Evaluation of the use of partition coefficients and molecular surface properties as predictors of drug absorption: a provisional biopharmaceutical classification of the list of national essential medicines of Pakistan

*Shawahna R. Rahman NU.

Department of Pharmacy, Faculty of Pharmacy and Alternative Medicine, The Islamia University of Bahawalpur, Pakistan.

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ABSTRACT

Background and the purpose of the study: Partition coefficients (log *D* and log *P*) and molecular surface area (PSA) are potential predictors of the intestinal permeability of drugs. The aim of this investigation was to evaluate and compare these intestinal permeability indicators.
Methods: Aqueous solubility data were obtained from literature or calculated using ACD/Labs and ALOGPS. Permeability data were predicted based on log *P*, log *D* at pH 6.0 (log $D_{6.0}$), and PSA.
Results: Metoprolol's log *P*, log $D_{6.0}$ and a PSA of <65 Å correctly predicted 55.9%, 50.8% and 54.2% of permeability classes, respectively. Labetalol's log *P*, log $D_{6.0}$, and PSA correctly predicted 54.2%, 64.4% and 61% of permeability classes, respectively. Log $D_{6.0}$ correlated well (81%) with Caco-2 permeability (P_{app}). Of the list of national essential medicines, 135 orally administered drugs were classified into biopharmaceutical classification system (BCS). Of these, 57 (42.2%), 28 (20.7%), 44 (32.6%), and 6 (4.4%) were class I, II, III and IV respectively.
Conclusion: Log $D_{6.0}$ showed better prediction capability than log *P*. Metoprolol as permeability internal standard was more conservative than labetalol.

Keywords: Biopharmaceutical classification system, Permeability, log *P*, log *D*, PSA.

INTRODUCTION

Systemic bioavailability of an orally administered drug is largely dependent on its physicochemical properties and dosage formulation factors (1). Sophisticated modeling of the kinetics and dynamics of drug processes in the gastrointestinal tract subsequently led to the advent of the biopharmaceutical classification system (BCS) (2). According to the biowaiver, any possible variation in the bioavailability of a rapidly dissolving and highly soluble drug is attributed to physiological conditions rather than formulation and hence there is no logic in conducting a bioequivalence testing for such formulation (2). BCS offers a framework for development of pharmaceutical formulations. It has been estimated that the pharmaceutical industry can save $35 million annually through the applications of BCS (3). Assignment of the solubility and permeability classes of a drug is a laborious task. Lately, computational models to predict aqueous solubility and permeability through biological membranes have received considerable attention. The use of physicochemical properties in predicting in vivo behavior of drugs has many advantages including cost reduction; better control over protocol, reproducibility and avoidance of risk presented to human volunteers usually encountered in the bioequivalence studies (4). Molecular surface properties and partition coefficients have been used actively in construction of quantitative structure activity relationship (QSAR) models to predict intestinal permeability (2, 5-6).

This study reports for the first time an evaluation and comparison of pH-dependent and pH-independent n-octanol/water partition coefficients (log *D* and log *P*) and polar surface area (PSA) in prediction of intestinal permeability of drugs. The log *D* at physiologically relevant pH of 6.0 (log $D_{6.0}$) was used to provisionally classify the orally administered drugs on the list of national essential medicines (NEML) of Pakistan into BCS.

MATERIAL AND METHODS

The present revision of the NEML contains 335 medicines of different pharmacological classes (7). The highest dose of drug products available in oral dosage forms, i.e. oral tablets and capsules, were used.

Solubility

The dose number (Do) was calculated using equation 1:

Correspondence: ramzi_shawahna@hotmail.com

$$Do = \frac{Mo/Vo}{C_s} \quad (1)$$

Where Mo is the highest dose strength (in mg), C_s is the solubility (mg/ml), and Vo equals to 250 ml (8). The most conservative data measures were used and experimental aqueous solubility data triumphed over predicted data. Experimental solubility data were obtained from Yalkowsky & He (9) and Drugbank (10) which in the later, data were originally from (11). Data reporting the pH and temperature at which the aqueous solubility of the compound was measured were favored. Solubility data for the rest of the drugs were calculated using ACD/Labs (ACD/Labs, version 6.0; Advanced Chemistry Development: Toronto, Canada) and ALOGPS (ALOGPS, version 2.1. The Virtual Computational Chemistry Laboratory, VCCLAB, Germany). The ionization constant (*pK*a) values were obtained from the literature (12).

Permeability

Log *D* and log *P* are linked through the equations 2 and 3:

For acids:

$$Log\ D = Log\ P - Log\ (1+10^{pH-pKa}) \quad (2)$$

For bases:

$$Log\ D = Log\ P - Log\ (1+10^{pKa-pKa}) \quad (3)$$

Both log *P* and log *D* values were calculated using ACD/Labs. Similarly, PSA values were estimated using ACD/Labs.

RESULTS AND DISCUSSION

Previously the orally administered drugs on the World Health Organization (WHO) essential medicine list (EML) were provisionally classified into BCS (13-14). The NEML contained 135 orally administered drugs. It has been emphasized that the maximal administered dose to solubility ratio has a central role in the BCS (15). The NEML contained 89 drugs in common with the WHO's EML while in term of doses, only 46 were similar (Table 1).

Solubility correlation and class assignment

Lindenberg and colleagues classified 61 drugs with certainty on the basis of reliable practical solubility data. A total of 59 drugs were in common with Lindenberg's list (13). ACD/Labs calculated solubility and predicted correctly that 51 (86.4%) of the solubility classes; whereas, data obtained from Drugbank and ALOGPS could correctly predict 76.3% and 78% of the drugs classified, respectively (Supplementary table 1). Solubility class assignment was compared to the WHO solubility classification (16). Of the 80 drugs in common, 66 drugs (82.5%) were classified in the same solubility classes, whereas, of the 14 drugs for which the solubility classes were different, 6 drugs were classified based on incomplete/ inconclusive data and 3 drugs had higher or lower doses on the NEML as compared to the WHO's EML (Supplementary table 2).

Of the 135 drugs on the NEML, 15 (11.1%) drugs were classified according to their experimental solubility data obtained from Yalkowsky & He, of which 7 (46.7%) were classified as high soluble drug while the rest of 8 (53.3%) were classified as low soluble drugs. Additionally, 33 drugs (24.4%) were classified based on the solubility data obtained from Drugbank. Of these, 29 (87.9%) were classified as high solubility drugs while the rest of 4 (12.1%) were classified as low soluble drugs. The rest of 87 drugs (64.4%) were classified according to the ACD/Labs predicted soluble, of which, 66 (75.9%) were classified as high soluble drugs and 21 (24.1%) drug were assigned to low solubility class drugs (Table 1).

Permeability correlation and class assignment

Kasim and colleagues used metoprolol as internal standard indicating high permeability (14). Palm and colleagues showed that PSA of <60 Å ensured complete intestinal absorption (6); however, Kelder and colleagues showed drug intestinal permeation predominated by passive diffusion and paracellular route for drugs with PSA of less than 120 Å (17). When log $D_{6.0}$ of -1.48, log *P* of 1.35, and a relaxed PSA of ≤65 Å were used to indicate high permeability of the 59 drugs in common with the Lindenberg's list, cutoffs correctly predicted the permeability class of 30, 33 and 32 drugs (50.8%, 54.2% and 55.9%), respectively (Supplementary table 3). The fraction absorbed (Fa) of metoprolol (≥95%) is considerably even more conservative than permeability criteria (≥90%) of the Food and Drug Administration (FDA) (18). The use of labetalol as high permeable internal standard (Fa ≥90%) was evaluated using log $D_{6.0}$ of -0.42, Log *P* of 2.31, and PSA of ≤95.6 Å. These cutoffs correctly predicted the permeability class of 38, 32, and 36 drugs (64.4%, 54.2% and 61%), respectively.

When WHO's classification (16) where compared with the current classification in table 1; of the 80 drugs in common, 62 drugs (77.5%) were classified in the same permeability classes, whereas, of the 18 drugs for which the permeability classes were different, 11 could be correctly classified by their PSA values (Supplementary table 2).

To further verify the suitability of the permeability class assignment based on log $D_{6.0}$, the Caco-2 monolayer permeability (P_{app}) values for a total of 22 drugs which were in common with a previous work

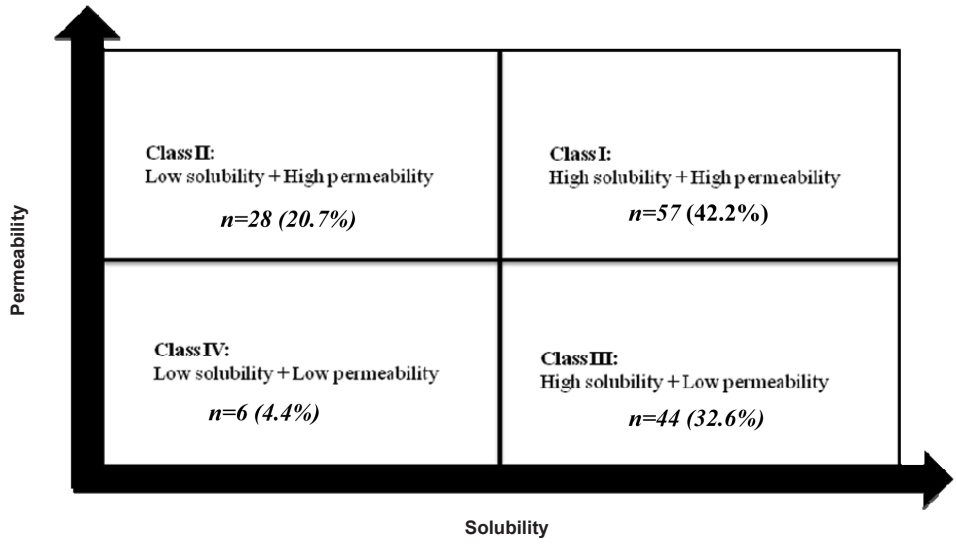

Figure 1. Biopharmaceutical classification system with drugs on the list of national essential medicines of Pakistan.

(13) were obtained; these values were basically compiled from the literature. The P_{app} value for labetalol was obtained from literature (15). Log $D_{6.0}$ correctly predicted the permeability class for 18 (81.8%) of the 22 drugs (Supplementary table 4). Furosemide, hydrochlorthiazide, saquinavir, and sulphasalazine were false positives. Similarly, the PSA of ≤95.6 Å (PSA of labetalol) correctly predicted the permeability class for 18 (81.8%) of the 22 drugs (Supplementary table 4). Acetylsalicylic acid, atenolol and zidovudine were false positives, whereas, digoxin was a false negative. The PSA of ≤65 Å correctly predicted only 15 (68.2%) out of the 22 drugs compared. In the study of Kasim and colleagues, the log *P* of metoprolol correctly predicted 18 of 28 (64%) drugs (5).

The permeability classes were assigned using log $D_{6.0}$ in comparison to labetalol which was used as internal standard. In this classification, 128 (94.8%) of the 135 drugs on the NEML were classified, of these, 83 (64.8%) were assigned in high permeability, while the rest of 45 (35.2%) were assigned in low permeability classes. The rest of the 7 (5.2%) were classified according to their PSA values. Of these 2 (28.6%) were classified as high permeability drugs, while the rest of 5 (71.4%) were classified as low permeability drugs. The final BCS classification of the 135 orally administered drugs on the NEML is given in table 1 and class distribution is shown in figure 1.

Literature often reported solubility data at room temperature. In contrast, the current solubility classification methodology yielded an acceptable accuracy of 86.4% and 78.3% for ACD/Labs and Drugbank solubility values respectively. Moreover, the current classification of solubility criteria were conservative since the solubility usually increases as a function of temperature, therefore, the solubility values at 37°C would be higher than the values used. In vivo human permeability investigations are expensive in terms of financial resources and technical allocations; and moreover are time consuming. Several reports described a certain correlation between physicochemical properties of drug molecules with intestinal absorption (6, 19-22). Linnankoski and colleagues suggested that passive diffusion predominates the routes of intestinal administration for the majority of the drugs (20). Although influx and efflux transporters have an important role in the absorption of some drugs, interestingly, for the majority of drugs the active transport is actually negligible (20). Most of the drugs available in the market are ionizable molecules; therefore, passive diffusion of these ionizable drugs is partly governed by their pKa values. Consequently, log *D* at physiologically relevant pH should better reflect the overall distribution (ionized and unionized) of a drug (22, 23).

Recently, labetalol was suggested as a better internal standard in the permeability comparisons (24). The effective intestinal permeability (P_{app}) is typically the parameter reflecting both the rate and extent of intestinal absorption. In the current classification, labetalol was used as internal standard. In accordance with results of this study, Winiwater and colleagues found a correlation between P_{app}, log *D* at pH of 5.5, PSA and hydrogen bond donors, the use of log $D_{6.0}$ gave better predictions than log *P* (22). Similarly, Linnankoski and colleagues established a correlation between the intestinal absorption rate constant (K_a) with log $D_{6.0}$ and PSA (20).

Table 1. BCS classification of the orally administered drugs on the list of national essential medicines (NEML) of Pakistan with their therapeutic classes, maximum doses, experimental water solubility, predicted aqueous solubility (ACD/Labs), pH dependent solubility (pKa), log $D_{6.0}$, calculated PSA, and interaction with transporters in the intestine.

Provisional biopharmaceutical classification of drugs on the list of national essential medicines (NEML) of Pakistan.

			Solubility					Permeability			BCS classification		
Drug	**Therapeutic class**	**Maximum dose (mg)**	**Do[1]**	**Do[2]**	**Do[3]**	**pKa**		**Log $D_{6.0}$ ¶**	**PSA[¥]**	**Transporters interaction‡**	**Solubility class**	**Permeability class**	**BCS Class**
						HA[†]	**BH+[†]**						
Acetylsalicylic acid	NSAID	300	NA		0.0012	3.48		-1.24	63.6	Pgp	High	Low	III
Acyclovir	Antiviral	200	NA		2.1	9.18	1.89	-1.76	109.83	OATP1, OATP3, OCT1	Low	Low	IV
Albendazole	Anthelmintic	200	NA		13.3	10.46	5.62	2.87	92.31	BCRP	Low	High	II
Allopurinol	anti-gout	300	NA		0.03	9.2	2.4	-3.81	74.69	NA	High	Low	III
Amiloride	Diuretic	5	NA		0.16	8.58	1.58	1.07	156.79	NA	High	High	I
Aminophylline	Antiasthmatic	200	NA	0.00002		NA		NA	192	NA	High	Low	III
Amiodarone	Antiarrhythmic	200	1.1				9.37	6.29	42.7	MDR1	Low	High	II
Amitryptyline	Antipsychotic	50	NA		0.14		9.24	2.08	3.24	NA	High	High	I
Amlodipine	Antihypertensive	5	NA	0.001			8.73	1.43	99.9	MDR1	High	High	I
Amoxicillin	Antibacterial	500	NA		6.66	2.61	6.93	-1.93	158.26	PEPT1	Low	Low	IV
Amphotericin B	Antifungal	100	0.5			3.96	8.13	NA	320	NA	High	Low	III
Ampicillin	Antibacterial	500	0.2			2.61	6.79	-1.21	138	PEPT1, OCTN2	High	Low	III
Anastrozole	Anticancer	1	NA	0.008			4.78	0.77	78.3	NA	High	High	I
Atenolol	Antihypertensive	100	NA		0.0004	13.88	9.17	-2.73	84.58	MDR1	High	Low	III
Atropine sulphate	Antispasmodic	1	NA		6.76E-06		9.88	-1.52	49.77	NA	High	Low	III
Azathioprine	Anticancer	50	1.5				0.25	-0.54	143	NA	Low	Low	IV
Bromocriptine	Antiparkinsonism	2.5	NA	0.11		9.61	6.45	4.52	118	MDR1	High	High	I
Busulphan	Anticancer	0.5	NA	1.20E-07		NA		-0.52	104	NA	High	Low	III
Baptopril	Antihypertensive	50	NA		0.0002	3.82		-2.02	96.41	MDR1: PEPT1	High	Low	III
Carbamazepine	Antiepileptic	200	NA		10	13.94		2.67	46.33	MDR1	Low	High	II
Carbidopa	Antiparkinsonism	25	NA	0.1		3.4	7.91	-2.71	116	NA	High	Low	III
Cefixime	Antibacterial	100	NA	0.03		2.1	2.86	-3.72	238	NA	High	Low	III
Cefuroxime	Antibacterial	250	NA	3.52		2.59		-4.47	199	PEPT1	Low	Low	IV
Cephalexin	Antibacterial	500	0.04			3.12	6.8	-2.22	138	PEPT1, PEPT2, OCTN2	High	Low	III
Cephradine	Antibacterial	500	0.25			3.12	6.99	-1.53	138	OAT1, OCTN2, PEPT1	High	Low	III
Chlorambucil	Anticancer	2	0.01			4.86	3.66	1.52	40.5	MRP1	High	High	I
Chloramphenicol	Antibacterial	250	NA		4.3	11.03		1.02	115.38	NA	Low	High	II
Chloroquine	Antimalarial	150	NA		0.02		10.48	1.2	28.16	MDR1	High	High	I

Table 1 (Cont)

Drug	Therapeutic class	Maximum dose (mg)	Solubility					Permeability			BCS classification		
						pKa							
			Do[1]	Do[2]	Do[3]	HA[†]	BH+[†]	Log $D_{6.0}$ ¶	PSA[¥]	Transporters interaction[‡‡]	Solubility class	Permeability class	BCS Class
Chlorpheniramine	Antiallergic	4	NA		0.0003		9.33	0.49	16.13	NA	High	High	I
Chlorpromazine	Antipsychotic	100	NA		0.44		9.43	2.28	31.78	MDR1, OCT1	High	High	I
Cimetidine	Antiulcer	400	NA		0.14		6.73	-1.14	114.19	MDR1, OAT1, OAT3, OCT1, OCT3, OCTN2	High	Low	III
Ciprofloxacin	Antibacterial	250	NA		0.77	2.74	8.76	-1.07	72.88	MDR1	High	Low	III
Clofazimine	Antileprosy	100	NA		412.4		6.24	5.72	39.99	MDR1	Low	High	II
Clomipramine	Antipsychotic	25	NA		0.09		9.49	2.58	6.48	MDR1	High	High	I
Clofazimine	Antileprosy	100	NA		412.4		6.24	5.72	39.99	MDR1	Low	High	II
Cloxacillin	Antibacterial	250	NA		0.07	NA		-0.81	138.04	PEPT1	High	Low	III
Colchicine	anti-gout	0.5	NA		0.03	NA		0.92	83.09	MDR1, OCT3	High	High	I
Cyclizine	Antihistamine	50	NA	0.2			7.46	1.83	6.5	NA	High	High	I
Cyclophosphamide	Anticancer	50	NA		0.002		4.09	0.23	51.38	MDR1	High	High	I
Cyclosporin	Immunosuppressent	100	10			NA		NA	279	BCRP, MDR1, MRPs, OATP1B1	Low	Low	IV
Dapsone	Antileprosy	50	NA		0.57		1.24	0.94	94.56	NA	High	High	I
Dexamethasone	Antiallergic	0.5	NA		0.04	12.14		1.87	94.83	MDR1, OATP1A2	High	High	I
Diazepam	Sedative	10	NA		2		3.4	2.96	32.67	MDR1	Low	High	II
Didanosine (ddi)	Antiretroviral	400	NA		0.81	8.67	1.98	-1.33	83.81	NA	High	Low	III
Digoxin	Cardiostimulant	0.25	NA		0.002	13.5		0.85	203.06	MDR1, OATP1B3, OATP1C1, OATP4C1, OST	High	High	I
Diloxanide	Anti-Amoebic	500	NA		1.08	NA		1.62	40.54	NA	Low	High	II
Diltiazem	Calcium channel blocker	180	NA	0.006			8.91	2.64	84.4	MDR1	High	High	I
Doxycycline	Antibacterial	100	NA		0.54	4.5	9.32	-3.06	181.62	OAT1, OAT3, OAT4	High	Low	III
Efavirenz	Antiretroviral	50	NA		376.6	7.92		4.84	38.33	NA	Low	High	II
Enalapril	Antihypertensive	10	NA	0.002		3.75	5.5	-0.12	95.9	MDR1, OATP1A2, PEPT1	High	High	I
Ergometrine	Oxytotic	0.25	NA		0.00018	NA		-0.54	68.36	MDR1	High	Low	III
Ergotamine	Antimigraine	1	NA		0.4	9.62	7.2	1.99	118.21	MDR1	High	High	I
Erythromycin	Antibacterial	500	NA		0.08	13.08	8.14	0.72	193.91	MDR1, MRP1, OAT2, OATP1A2	High	High	I
Ethambutol	Anti-tuberculosis	400	NA		0.0016		9.6	-3.23	64.52	NA	High	Low	III
Ethosuximide	Antiepileptic	250	NA		0.042		9.7	0.38	46.17	NA	High	High	I
Etoposide	Anticancer	100	2			9.95		1.96	161	BCRP, MDR1-3,6,7,	Low	High	II

Table 1 (Cont)

Drug	Therapeutic class	Maximum dose (mg)	Solubility					Permeability			BCS classification		
						pKa							
			Do[1]	Do[2]	Do[3]	HA[†]	BH+[†]	Log $D_{6.0}$ ¶	PSA[¥]	Transporters interaction‡	Solubility class	Permeability class	BCS Class
Fluoxetine	Antipsychotic	20	NA	0.002		10.05		NA	21.3	MDR1	High	High	I
Flutamide	Anticancer	250	NA	0.42		13.12		NA	74.9	NA	High	High	I
Furosemide	Diuretic	40	NA		0.02	3.04		0.26	131.01	MRP2, OAT1, OAT3, OAT4, OCTN2	High	High	I
Gemfibrozil	Antihyperlipidemia	300	NA	0.12		4.75		2.14	46.5	NA	High	High	I
Glibenclamide	Antidiabetic	5	NA		1	NA		2.75	121.98	BSEP, MDR1, MRP1, OATP2B1	High	High	I
Griseofulvin	Antifungal	500	NA		2985.07	NA		3.53	71.06	NA	Low	High	II
Haloperidol	Antipsychotic	5	NA		0.006	13.9	8.25	0.82	40.54	MDR1	High	High	I
Hydralazine	Antihypertensive	25	NA		0.08	NA		0.56	63.83	NA	High	High	I
Hydrochlorthiazide	Diuretic	50	NA		0.48	8.95		-0.07	135.12	NA	High	High	I
Ibuprofen	NSAID	600	NA		1.17	4.41		2.12	37.3	MDR1, MRP1, MRP3, OAT1-4	Low	High	II
Imipramine	Antipsychotic	25	5.5				9.49	1.85	6.5	MDR1, OCT2, OCT3	Low	High	II
Indinavir	Antiretroviral	400	NA		53.3		5.73	2.76	118.03	MDR1, MRP1, MRP2, OATP1A2, OATP1B1	Low	High	II
Indomethacin	NSAID	25	6.25			4.17		0.3	68.5	MDR1, MRP1-8, OAT1-4	Low	High	II
Isoniazid	Anti-tuberculosis	300	NA		0.01	11.27	3.79	-0.89	68.01	NA	High	Low	III
Isosorbide dinitrate	Antianginal	10	NA		4.82E-05	NA		-1.75	58.92	NA	High	Low	III
Labetalol	Antihypertensive	200	NA	0.04		7.91	9.2	-0.42	95.6	NA	High	High	I
Lamivudine (3tc)	Antiretroviral	150	NA		0.17	13.83	4.41	-0.71	113.45	BCRP, MRP1	High	Low	III
Levamisole	Anthelmintic	40	NA		0.0067		8.81	-0.15	40.9	NA	High	High	I
Levodopa	Antiparkinsonism	250	NA		0.09	2.24	9.3	-0.27	103.78	NA	High	High	I
Lisinopril	Antihypertensive	20	NA	0.02		2.18	10.51	-1.32	133	MDR1, PEPT1	High	Low	III
Losartan	Antihypertensive	25	NA	0.49		4.24	3.1	0.89	92.5	MDR1, OAT1	High	High	I
Mebendazole	Anthelmintic	100	NA		20	10.29	5.02	2.77	84.08	MDR1	Low	High	II
Mercaptopurine	Anticancer	50	0.03			8.46	2.4	0.37	85.2	MRP4, MRP5	High	High	I
Metformin	Antidiabetic	500	NA		0.002		13.1	-4.31	88.99	OCT1, OCT2	High	Low	III
Methionine	Antidote	250	NA		0.04	2.23	9.26	-2.13	88.6	OCTN2	High	Low	III
Methotrexate	Anticancer	10	NA	6.20E-05		3.54	5.09	NA	211	BCRP, MDR1, MRP1-7, OAT1-4, OATP1B1, OATP1B3, OATP1C1	High	Low	III
Methyldopa	Antihypertensive	500	NA		0.3	2.28	9.3	-2.37	103.78	PEPT1	High	Low	III
Metoclopramide	Antiemetic	10	NA		0.0002	13.28	9.62	-7.8	67.59	NA	High	Low	III

Table 1 (Cont)

Drug	Therapeutic class	Maximum dose (mg)	Solubility					Permeability			BCS classification		
						pKa							
			Do[1]	Do[2]	Do[3]	HA[†]	BH+[†]	Log $D_{6.0}$ ¶	PSA[¥]	Transporters interaction[‡‡]	Solubility class	Permeability class	BCS Class
Metronidazole	Anti-Amoebic	400	NA		0.2		2.58	-1.01	78.94	NA	High	Low	III
Morphine	Analgesic	30	NA		0.0005	9.72	8.14	-1.77	52.93	MDR1	High	Low	III
Nalidixic acid	Antibacterial	500	NA		0.73	1.2	5.95	0.33	70.5	NA	High	High	I
Nelfinavir	Antiretroviral	250	NA		291.54	9.58	7.53	5.44	127.2	BCRP, MDR1, OATP1A2, OATP1B1	Low	High	II
Neostigmine	Antidote	15	NA		0.00019	NA		-3.03	29.54	MDR1	High	Low	III
Nevirapine	Antiretroviral	200	NA		1.37	10.93	4.74	1.84	58.12	NA	Low	High	II
Niclosamide	Anthelmintic	500	NA		1801.8	NA		5.4	95.15	NA	Low	High	II
Nitrofurantoin	Antibacterial	100	NA		0.28	7.69	1.2	-0.41	120.73	NA	High	High	I
Nitroglycerin	Antianginal	6.4	0.02			NA		2.22	165	NA	High	High	I
Nystatin	Antifungal	200	NA		26.6	NA		-0.42	319.61	NA	Low	High	II
Omeprazole	Antiulcer	20	NA	0.004		9.08	4.61	2.15	96.3	BCRP, MDR1, MRP3	High	High	I
Paracetamol	Analgesic	500	NA		0.19	9.86		0.34	49.33	NA	High	High	I
Penicillamine	Antidote	250	NA		0.096	2.13	11.54	-1.57	102.12	NA	High	Low	III
Phenobarbital	Antiepileptic	30	NA		0.18	7.88		1.66	75.27	NA	High	High	I
Phenoxymethylpenicillin	Antibacterial	500	NA		0.02	2.62		-1.47	121.24	NA	High	Low	III
Phenytoin	Antiepileptic	100	NA		4	8.33		2.52	58.2	MDR1, MRP2	Low	High	II
Prazosin	Antihypertensive	2	NA	0.016			6.47	-1.25	107	BCRP, MDR1, OCT1-3	High	Low	III
Prednisolone	Antiallergic	5	NA		0.15	12.47		1.49	94.83	MDR1	High	High	I
Primaquine	Antimalarial	7.5	NA		0.00015		10.38	-0.41	60.17	NA	High	High	I
Procainamide	Antiarrythmic	250	NA	0.017			9.86	-1.43	58.4	MDR1, OATP1A2, OCT1-3, OCTN1,2	High	Low	III
Procarbazine	Anticancer	50	NA	0.0006			7.46	0.11	53.2	NA	High	High	I
Prochlorperazine	Antipsychotic	5	1.34				7.82	2.42	35	NA	Low	High	II
Procyclidine	Antiparkinsonism	5	NA	2.03			10.48	0.84	23.5	NA	Low	High	II
Promethazine	Antiallergic	25	NA		0.04		8.98	2.04	31.78	MDR1	High	High	I
Propranolol	Antihypertensive	160	NA		0.01	13.84	9.14	0.28	41.49	MDR1, NTCP, OCT2	High	High	I
Propylthiouracil	Anticancer	100	NA		0.2	7.63	0.54	1.36	73.22	NA	High	High	I
Pyrantel	Anthelmintic	250	NA		0.012		10.97	-0.49	43.84	NA	High	Low	III
Pyrazinamide	Anti-tuberculosis	500	NA		0.09		13.91	-0.37	68.87	NA	High	High	I
Pyridostigmine	Muscle relaxant	60	NA		0.0005	NA		-4.31	29.54	NA	High	Low	III

Table 1 (Cont)

Drug	Therapeutic class	Maximum dose (mg)	Solubility					Permeability			BCS classification		
			Do[1]	Do[2]	Do[3]	pKa		Log $D_{6.0}$ ¶	PSA[¥]	Transporters interaction‡	Solubility class	Permeability class	BCS Class
						HA[†]	BH+[†]						
Quinidine	Antiarrythmic	200	5.7			13.05	9.13	1.35	45.6	BSEP, MDR1, OAT3, OATP1A2, OATP1B1, OCT1,2, OCTN1,2	Low	High	II
Quinine	Antimalarial	200	NA		0.03	13.05	9.13	0.54	45.59	MDR1, OATP1A2, OATP1C1, OCT1,2, OCTN1,2	High	High	I
Risperidone	Antipsychotic	3	NA	0.017		7.91		1.01	61.9	NA	High	High	I
Rifampicin	Anti-tuberculosis	600	NA	1.71		NA		-1.75	217	MDR1, MRP1,2,5, OATP1A2, OATP1B1, OATP1B3, OATP2B1	Low	Low	IV
Ritonavir	Antiretroviral	100	NA		1063.8	11.47	3.48	5.28	202.26	BCRP, MDR1, MRP1,2, OATP1A2, OATP1B1	Low	High	II
Salbutamol	Antiasthmatic	4	NA		0.000016	9.83	9.22	-2.84	72.72	NA	High	Low	III
Saquinavir	Antiretroviral	200	NA		16	NA		2.84	166.75	BCRP, MDR1,2, OATP1A2, OATP1B1	Low	High	II
Selegiline	Antiparkinsonism	5	NA	0.78			7.53	1.42	3.2	MDR1	High	High	I
Spironolactone	Diuretic	100	NA		44.3	NA		3.12	85.74	MDR1	Low	High	II
Stavudine (D4T)	Antiretroviral	40	NA		0.009	9.57		-0.86	78.87	NA	High	Low	III
Sulphasalazine	Antibacterial	500	NA		0.29	2.88	1.86	0.35	149.69	NA	High	High	I
Tamoxifen	Anticancer	20	NA	479.04			8.69	6.2	12.5	BCRP, BSEP, MDR1	Low	High	II
Theophylline	Antiasthmatic	270	NA		0.25	8.6	1.05	-0.18	69.3	NA	High	High	I
Thioacetazone	Anti-tuberculosis	50	NA	0.2		NA		NA	112	NA	High	Low	III
Thioguanine (6 thioguanine)	Anticancer	40	NA	0.004		7.44	3.09	-0.4	111	MRP4	High	High	I
Tinidazole	Antifungal	500	NA	0.0004		NA		-0.27	106	NA	High	High	I
Trifluperazine	Antipsychotic	5	NA	1.63			7.82	4.04	35	NA	Low	High	II
Trimethoprim	Antibacterial	300	NA		0.17		7.34	-0.42	105.51	MDR1	High	High	I
Valproic acid	Antiepileptic	300	NA		0.005	4.82		-1.65	100.27	OAT3, OCTN2	High	Low	III
Verapamil	Antihypertensive	240	NA	0.85			9.03	2.91	64	BCRP, BSEP, MDR1, MRP1-4,7, OATP1A2, OCT1, OCTN1,2, PGP	High	High	I
Warfarin	Anti-coagulant	5	NA		0.01	4.5		1.91	63.6	NA	High	High	I
Zalcitabine (DDC)	Antiretroviral	0.75	NA	4.96E-07			4.47	-1.51	88.2	NA	High	Low	III
Zidovudine (ZDV)	Antiretroviral	100	NA		0.1	NA		-0.53	91.23	PEPT1	High	Low	III

1- Do (dose number) calculated from solubility data taken from ref. (9); 2 Do (dose number) calculated from solubility data taken from ref. (10); 3 Do (dose number) calculated from predicted solubility data, ACD/Labs; * The maximal dose strength on the list of national essential medicines of Pakistan; † pKa values were taken from ref. 12; ¶ Calculated log $D_{6.0}$ values at pH 6 using ACD/Labs; ¥ PSA calculated from ACD/Labs; ‡ Transporter interaction taken from ref. 25;BCRP: Breast cancer resistance protein; BSEP: Bile salt export pump; MDR: Multidrug transporter; MRP: Multidrug resistance protein; NA: not available; OAT: Organic anion transporter; OATP: Organic anion-transporting polypeptide; OCTN: Organic cation transporter; OST: Organic solute transporter; PEPT: Peptide transporter; Pgp: P-glycoprotein.

Supplementary table 1: Solubility data correlation: ACD/Labs, experimental water solubility DrugBank, ALOGPS and reliable experimental solubility.

Drug	Dose (mg)	Do[1]	D[2]	D [3]	Solubility Class 1	Solubility Class 2	Solubility Class 3	Reliable experimental solubility[Θ]
Abacavir	300	2.9268293	0.0155844	0.99173554	Low	High	High	High
Acetylsalicylic Acid	500	0.002	0.4347826	1.36986301	High	High	Low	High
Aciclovir	200	2.1052632	0.4938272	0.08810573	Low	High	High	High
Allopurinol	100	0.0101807	0.7029877	0.06802721	High	High	High	High
Amiloride	5	0.1666667		0.01639344	High		High	High
Atenolol	100	0.0004	0.0296296	0.93240093	High	High	High	High
Captopril	25	0.0001		0.02212389	High		High	High
Carbamazepine	200	10	45.19774	5.26315789	Low	Low	Low	Low
Chloramphenicol	250	4.3478261	0.4	2.1691974	Low	High	Low	High
Chloroquine	150	0.0220345	56.603774	34.2857143	High	Low	Low	High
Cimetidine	200	0.0722022	0.16	0.98039216	High	High	High	High
Cloxacillin	1000	0.2805049	287.76978	75.1879699	High	Low	Low	High
Codeine	30	0.0022822	0.0133333	0.20797227	High	High	High	High
Colchicine	0.5	0.0285714	4.44E-05	0.07246377	High	High	High	High
Cyclophosphamide	25	0.0011682	0.002	0.00662252	High	High	High	High
Dapsone	100	1.1428571	1.0526316	1.4084507	Low	Low	Low	Low
Diazepam	5	1	0.4	1.63934426	High	High	Low	High
Digoxin	0.625	0.0054348		0.01968504	High		High	High
Doxycycline	100	0.5405405	0.6349206	0.7751938	High	High	High	High
Ergotamine	1	0.4		0.01793722	High		High	High
Fluconazole	50	0.7407407	200	0.14388489	High	Low	High	High
Furosemide	40	0.0230548	26.666667	1.3559322	High	Low	Low	Low
Griseofulvin	250	1492.5373	115.74074	19.8412698	Low	Low	Low	Low
Hydralazine	50	0.1724138		0.07575758	High		High	High
Hydrochlorothiazide	25	0.2439024	0.1428571	0.04464286	High	High	High	High
Ibuprofen	400	0.7804878	32.653061	23.3918129	High	Low	Low	Low
Indinavir	400	53.333333	106.66667	33.1950207	Low	Low	Low	Low
Levodopa	250	0.0942507	23.562677	0.3030303	High	Low	High	High
Levonorgestrel	0.75	0.4207574	1.4705882	0.51457976	High	Low	High	High
Levothyroxine	0.1	0.0997506	0.0038095	0.04454343	High	High	High	High
Metformin	500	0.002		0.88888889	High		High	High
Methyldopa	250	0.149925	1	0.44247788	High	High	High	High
Metronidazole	500	0.2816901	84.459459	0.008	High	Low	High	High
Nelfinavir	250	291.54519		523.560209	Low		Low	Low
Nifedipine	10	1.3333333		2.25988701	Low		Low	Low
Nitrofurantoin	100	0.2857143	5.0327126	0.96385542	High	Low	High	Low
Paracetamol	500	0.1966568	0.1428571	0.48192771	High	High	High	High
Penicillamine	250	0.0968054	0.009009	0.21505376	High	High	High	High
Penicillin V	250	0.0125723	1	2.20264317	High	High	Low	High
Phenobarbital	100	0.625	0.3603604	1.44927536	High	High	Low	High
Phenytoin	100	4	12.5	5.62587904	Low	Low	Low	Low
Prednisolone	5	0.1538462	0.0896861	0.08368201	High	High	High	High
Primaquine	15	0.0003165		1.06382979	High		Low	High

Supplementary table 1 (Cont)

Drug	Dose (mg)	D[1]	D[2]	D[3]	Solubility Class 1	Solubility Class 2	Solubility Class 3	Reliable experimental solubility[Θ]
Promethazine	25	0.0478469		4.08163265	High		Low	High
Propranolol	40	0.0029602	2.2857143	2.01511335	High	Low	Low	High
Propylthiouracil	50	0.1149425	0.1666667	0.42918455	High	High	High	High
Pyrazinamide	400	0.0759734	0.1066667	0.01707577	High	High	High	High
Pyridostigmine	60	0.0005417		0.23076923	High		High	High
Riboflavin	5	0.0001868	0.2361275	0.0304414	High	High	High	High
Ritonavir	100	1063.8298		317.460317	Low		Low	Low
Salbutamol	4	0.000016	5.3333333	0.00744186	High	Low	High	High
Saquinavir	200	16		323.88664	Low		Low	Low
Stavudine	40	0.0091376	0.016	0.00395062	High	High	High	High
Sulfamethoxazole	400	1.509434	2.6229508	3.48583878	Low	Low	High	Low
Theophylline	300	0.2836879	0.24	0.05240175	High	High	High	High
Thiamine	50	0.0009126	0.0004	13.0718954	High	High	Low	High
Trimethoprim	200	0.1152738	0.0661157	1.30081301	High	High	Low	Low
Valproic Acid	500	0.0091258	0.004	130.718954	High	High	Low	Low
Zidovudine	300	0.3243243	0.024	0.07361963	High	High	High	High

1-Do (dose number) calculated from predicted solubility data, ACD/Labs; 2 Do (dose number) calculated from solubility data obtained from DrugBank database; 3 Do (dose number) calculated from predicted solubility data, ALOGPS; Θ Reliable experimental solubility, were taken from ref. 13.

Supplementary table 2: Solubility and permeability classification comparing the list of national essential medicines (NEML) of Pakistan and classification of the WHO's essential medicines model list (EML)

Drug	WHO¶ Dose (mg)	NEML Dose (mg)	WHO¶ Solubility class	NEML Solubility class	Comment	WHO ¶ Permeability class	NEML Permeability class	Comment
Acetylsalicylic acid	500	300	High	High		High	Low	Classified as low permeability drug based on reliable data*; log $D_{6.0}$ indicated low permeability, whereas, PSA was lower than that of labetalol
Aciclovir	200	200	High	Low		Low	Low	
Albendazole	400	200	Low	Low		inconclusive	High	
Allopurinol	100	300	High	High		High	Low	Classified as low permeability drug based on reliable data*; log $D_{6.0}$ indicated low permeability, whereas, PSA was lower than that of labetalol
Amiloride	**5**	**5**	High	High		High	High	
Amitriptyline	25	50	High	High		High	High	

Supplementary table 2 (Cont)

Drug	WHO¶ Dose (mg)	NEML Dose (mg)	WHO¶ Solubility class	NEML Solubility class	Comment	WHO ¶ Permeability class	NEML Permeability class	Comment
Amlodipine	5	5	High	High		High	High	
Amoxicillin	500	500	High	Low	classified as high solubility based on incomplete data*	High	Low	Classified as high permeability based on incomplete data*; both log $D_{6.0}$ and PSA indicated low permeability
Atenolol	100	100	High	High		Low	Low	
Carbamazepine	200	200	Low	Low		High	High	
Cefixime	400	100	Low	High	NEML dose is lower than that of WHO	inconclusive	Low	
Chloramphenicol	250	250	High	Low		Low	High	Classified as low permeability based on reliable data*; PSA can indicate low permeability
Chloroquine	150	150	High	High		High	High	
Chlorphenamine	4	4	High	High		inconclusive	High	
Chlorpromazine	100	100	High	High		inconclusive	High	
Ciprofloxacin	250	250	High	High		inconclusive	Low	
Clomipramine	25	25	High	High		inconclusive	High	
Cloxacillin	1000	250	High	High		Low	Low	
Dapsone	100	50	Low	High	NEML dose is lower than that of WHO	High	High	
Diazepam	5	10	High	Low	NEML dose is higher than that of WHO	High	High	
Didanosine	400	400	High	High		Low	Low	
Digoxin	0.25	0.25	High	High		High	High	
Diloxanide	500	500	Low	Low		inconclusive	High	
Doxycycline	100	100	High	High		High	Low	Classified as low permeability drug based on reliable data*; both log $D_{6.0}$ and PSA indicated low permeability
Efavirenz	200	50	Low	Low		inconclusive	High	
Enalapril	2.5	10	High	High		Low	High	Both log $D_{6.0}$ and PSA indicated high permeability

Supplementary table 2 (Cont)

Drug	WHO¶ Dose (mg)	NEML Dose (mg)	WHO¶ Solubility class	NEML Solubility class	Comment	WHO ¶ Permeability class	NEML Permeability class	Comment
Erythromycin	250	500	Low	High	classified as low solubility based on incomplete data*	Low	High	Classified as low permeability based on incomplete data*; PSA can indicate low permeability
Ethambutol	400	400	High	High		Low	Low	
Furosemide	40	40	Low	High		inconclusive	High	
Glibenclamide	5	5	Low	High	classified as low solubility based on inconclusive data*	inconclusive	High	
Griseofulvin	250	500	Low	Low		High	High	
Haloperidol	2	5	inconclusive	High		Low	High	
Hydralazine	50	25	High	High		Low	High	Classified as low permeability drug based on reliable data*; both log $D_{6.0}$ and PSA indicated high permeability
Hydrochlorothiazide	25	50	High	High		Low	High	Classified as low permeability drug based on reliable data*; PSA can indicate low permeability
Ibuprofen	400	600	Low	Low		High	High	
Indinavir sulfate	400	400	Low	Low		inconclusive	High	
Isoniazid	300	300	High	High		inconclusive	Low	
Isosorbide dinitrate	5	10	High	High		inconclusive	Low	
Lamivudine	150	150	High	High		High	Low	Both log $D_{6.0}$ and PSA indicated low permeability
Levamisole	150	40	High	High		inconclusive	High	
Levodopa	250	250	High	High		High	High	
Carbidopa	25	25	High	High		inconclusive	Low	
Mebendazole	500	100	Low	Low		inconclusive	High	
Dl-methionine	250	250	High	High		High	Low	Classified as high permeability based on incomplete data*; PSA can indicate high permeability
Metformin	500	500	High	High		Low	Low	
Methyldopa	250	500	High	High		Low	Low	

Supplementary table 2 (Cont)

Drug	WHO¶ Dose (mg)	NEML Dose (mg)	WHO¶ Solubility class	NEML Solubility class	Comment	WHO ¶ Permeability class	NEML Permeability class	Comment
Metoclopramide	10	10	High	High		Low	Low	
Metronidazole	500	400	High	High		High	Low	Classified as high permeability drug based on reliable data*; PSA can indicate low permeability
Morphine	10	30	High	High		inconclusive	Low	
Nelfinavir	250	250	inconclusive	Low		inconclusive	High	
Neostigmine	15	15	High	High		Low	Low	
Nevirapine	200	200	Low	Low		High	High	
Niclosamide	500	500	Low	Low		inconclusive	High	
Nitrofurantoin	100	100	Low	High		High	High	
Nystatin	200	200	inconclusive	Low		inconclusive	High	
Paracetamol	500	500	High	High		High	High	
Penicillamine	250	250	High	High		Low	Low	
Phenobarbital	100	30	High	High		High	High	
Penicillin v	250	500	High	High		High	Low	Classified as high permeability drug based on reliable data*; both log $D_{6.0}$ and PSA indicated low permeability
Phenytoin	100	100	Low	Low		High	High	
Prednisolone	25	5	High	High		High	High	
Primaquine	15	7.5	High	High		High	High	
Promethazine	25	25	High	High		High	High	
Propranolol	40	160	High	High		High	High	
Propylthiouracil	50	100	High	High		High	High	
Pyrantel	250	250	Low	High	classified as low solubility based on inconclusive data*	inconclusive	Low	
Pyrazinamide	400	500	High	High		inconclusive	High	
Quinine	300	200	High	High		High	High	
Rifampicin	300	600	Low	Low		High	Low	Classified as high permeability based on incomplete data*; both log $D_{6.0}$ and PSA indicated low permeability
Ritonavir	100	100	Low	Low		inconclusive	High	
Salbutamol	4	4	High	High		High	Low	
Saquinavir	200	200	Low	Low		inconclusive	High	
Spironolactone	25	100	inconclusive	Low		inconclusive	High	

Supplementary table 2 (Cont)

Drug	WHO¶ Dose (mg)	NEML Dose (mg)	WHO¶ Solubility class	NEML Solubility class	Comment	WHO ¶ Permeability class	NEML Permeability class	Comment
Stavudine (d4t)	40	40	High	High		High	Low	PSA can indicate high permeability
Sulphasalazine	500	500	Low	High	classified as low solubility based on inconclusive data*	Low	High	Inconclusive data*; PSA can indicate low permeability
Trimethoprim	200	300	Low	High		High	High	
Valproic acid	500	300	High	High		High	Low	Classified as high permeability drug based on reliable data*; both log $D_{6.0}$ and PSA indicated low permeability
Verapamil	80	240	Low	High	classified as low solubility based on inconclusive data*	High	High	
Warfarin	5	5	High	High		High	High	
Zidovudine (zdv)	300	100	High	High		High	Low	Classified as high permeability drug based on reliable data*; PSA can indicate high permeability

* Ref. (13); ¶ Ref. (16)

Supplementary table 3: Comparison of Permeability prediction based on log *P*, log $D_{6.0}$ and PSA, by using metoprolol or labetalol as internal standard.

Drug	Log *P*	Log $D_{6.0}$	PSA	Internal standard: Metoprolol			Internal standard: Labetalol			Reliable experimental solubility$^{\Theta}$
				Log *P* cutoff "1.35"	Log $D_{6.0}$ cutoff "-1.48"	PSA cutoff "65"	Log *P* cutoff "2.31"	Log $D_{6.0}$ cutoff "-0.42"	PSA cutoff "95.6"	
Abacavir	0.72	0.03	96.95	Low	Low	Low	Low	High	Low	Low
Acetylsalicylic Acid	1.19	-1.24	63.6	Low	Low	High	Low	Low	High	Low
Aciclovir	-1.76	-1.76	109.83	Low	Low	Low	Low	Low	Low	Low
Allopurinol	-1.33	-3.81	74.69	Low	Low	Low	Low	Low	High	Low
Amiloride	1.08	1.07	156.79	Low	Low	Low	Low	High	Low	High
Atenolol	0.1	-2.73	84.58	Low	Low	Low	Low	Low	High	Low
Captopril	0.27	-2.02	96.41	Low	Low	Low	Low	Low	Low	Low
Carbamazepine	2.67	2.67	46.33	High	High	High	High	High	High	High
Chloramphenicol	1.02	1.02	115.38	Low	Low	Low	Low	High	Low	Low
Chloroquine	4.69	1.2	28.16	High	Low	High	High	High	High	High
Cimetidine	0.26	-1.14	114.19	Low	Low	Low	Low	Low	Low	Low
Cloxacillin	2.53	-0.81	138.04	High	Low	Low	High	Low	Low	Low
Codeine	1.2	-0.99	41.93	Low	Low	High	Low	Low	High	Low
Colchicine	0.92	0.92	83.09	Low	Low	Low	Low	High	High	Low
Cyclophosphamide	0.23	0.23	51.38	Low	Low	High	Low	High	High	High

Supplementary table 3 (Cont)

Drug	Log *P*	Log $D_{6.0}$	PSA	Internal standard: Metoprolol			Internal standard: Labetalol			Reliable experimental solubility[Θ]
				Log *P* cutoff "1.35"	Log $D_{6.0}$ cutoff "-1.48"	PSA cutoff "65"	Log *P* cutoff "2.31"	Log $D_{6.0}$ cutoff "-0.42"	PSA cutoff "95.6"	
Dapsone	0.94	0.94	94.56	Low	Low	Low	Low	High	High	High
Diazepam	2.96	2.96	32.67	High	High	High	High	High	High	High
Digoxin	0.85	0.85	203.06	Low	Low	Low	Low	High	Low	High
Doxycycline	-0.54	-3.06	181.62	Low	Low	Low	Low	Low	Low	High
Ergotamine	3.58	1.99	118.21	High	High	Low	High	High	Low	Low
Fluconazole	0.5	0.5	71.79	Low	Low	Low	Low	High	High	High
Furosemide	3	0.26	131.01	High	Low	Low	High	High	Low	Low
Griseofulvin	3.53	3.53	71.06	High	High	Low	High	High	High	High
Hydralazine	1	0.56	63.83	Low	Low	High	Low	High	High	Low
Hydrochlorothiazide	-0.07	-0.07	135.12	Low	Low	Low	Low	High	Low	Low
Ibuprofen	3.72	2.12	37.3	High	High	High	High	High	High	High
Indinavir	2.88	2.76	118.03	High	High	Low	High	High	Low	Low
Levodopa	-0.22	-0.27	103.78	Low	Low	Low	Low	High	Low	High
Levonorgestrel	3.92	3.92	37.3	High	High	High	High	High	High	High
Levothyroxine	5.93	3.38	92.78	High	High	Low	Low	High	High	Low
Metformin	-2.31	-4.31	88.99	Low	Low	Low	Low	Low	High	Low
Methyldopa	0.12	-2.37	103.78	Low	Low	Low	Low	Low	Low	Low
Metronidazole	-1.01	-1.01	78.94	Low	Low	Low	Low	Low	High	High
Nelfinavir	6.98	5.44	127.2	High	High	Low	Low	High	Low	Low
Nifedipine	2.97	2.96	110.45	High	High	Low	High	High	Low	High
Nitrofurantoin	-0.4	-0.41	120.73	Low	Low	Low	Low	High	Low	High
Paracetamol	0.34	0.34	49.33	Low	Low	High	Low	High	High	Low
Penicillamine	0.93	-1.57	102.12	Low	Low	Low	Low	Low	Low	Low
Penicillin V	1.88	-1.47	121.24	High	Low	Low	Low	Low	Low	High
Phenobarbital	1.67	1.66	75.27	High	High	Low	Low	High	High	High
Phenytoin	2.52	2.52	58.2	High	High	High	High	High	High	High
Prednisolone	1.49	1.49	94.83	High	High	Low	Low	High	High	High
Primaquine	2.67	-0.41	60.17	High	Low	High	High	High	High	High
Promethazine	4.78	2.04	31.78	High	High	High	High	High	High	Low
Propranolol	3.1	0.28	41.49	High	Low	High	High	High	High	High
Propylthiouracil	1.37	1.36	73.22	High	Low	Low	Low	High	High	Low
Pyrazinamide	-0.37	-0.37	68.87	Low	Low	Low	Low	High	High	High
Pyridostigmine	-4.31	-4.31	29.54	Low	Low	High	Low	Low	High	Low
Riboflavin	-2.02	-3.48	155.05	Low	Low	Low	Low	Low	Low	High
Ritonavir	5.28	5.28	202.26	High	High	Low	Low	High	Low	Low
Salbutamol	0.01	-2.84	72.72	Low	Low	Low	Low	Low	High	High
Saquinavir	4.44	2.84	166.75	High	High	Low	High	High	Low	Low
Stavudine	-0.86	-0.86	78.87	Low	Low	Low	Low	Low	High	High
Sulfamethoxazole	0.89	0.49	106.6	Low	Low	Low	Low	High	Low	High
Theophylline	-0.17	-0.18	69.3	Low	Low	Low	Low	High	High	High
Thiamine	-1.61	-1.65	100.27	Low	Low	Low	Low	Low	Low	Low
Trimethoprim	0.79	-0.42	105.51	Low	Low	Low	Low	High	Low	High
Valproic Acid	-1.61	-1.65	100.27	Low	Low	Low	Low	Low	Low	High
Zidovudine	-0.53	-0.53	91.23	Low	Low	Low	Low	Low	High	High

Supplementary table 4: Permeability data correlation: Log $D_{6.0}$ ACDLabs, PSA and experimental Caco-2 permeability coefficient (P_{app}).

Drug	P_{app}**	Permeability class	Log $D_{6.0}$¶	Permeability class	Prediction	PSA cutoff "95.6"	Prediction	PSA cutoff "65"	Prediction	Log *P* cutoff "1.35"	Prediction	Log *P* cutoff "2.31"	Prediction
Acetylsalicylic acid	2.4×10^{-6}	Low	-1.24	Low	c	High	fp	High	fp	Low	c	Low	c
Atenolol	5.3×10^{-7}	Low	-2.73	Low	c	High	fp	Low	c	Low	c	Low	c
Carbamazepine	2.15×10^{-5}	High	2.67	High	c	High	c	High	c	High	c	High	c
Chlorpheniramine	1.6×10^{-5}	High	0.49	High	c	High	c	High	c	High	c	High	c
Cimetidine	1.37×10^{-6}	Low	-1.14	Low	c	Low	c	Low	c	Low	c	Low	c
Dexamethasone	2.34×10^{-5}	High	1.87	High	c	High	c	Low	fn	High	c	Low	fn
Diazepam	3.34×10^{-5}	High	2.96	High	c	High	c	High	c	High	c	High	c
Digoxin	5×10^{-5}	High	0.85	High	c	Low	fn	Low	fn	Low	fn	Low	fn
Diltiazem	4.9×10^{-5}	High	2.64	High	c	High	c	Low	fn	High	c	High	c
Furosemide	3.33×10^{-6}	Low	0.26	High	fp	Low	c	Low	c	High	fp	High	fp
Griseofulvin	3.68×10^{-5}	High	3.53	High	c	High	c	Low	fn	High	c	High	c
Hydrochlorthiazide	5.1×10^{-7}	Low	-0.07	High	fp	Low	c	Low	c	Low	c	Low	c
Ibuprofen	5.25×10^{-5}	High	2.12	High	c	High	c	High	c	High	c	High	c
Indomethacin	2.04×10^{-5}	High	0.3	High	c	High	c	Low	fn	High	c	High	c
Labetalol	1.5×10^{-5}	Ref	-0.42	High	c	High	c	Low	fn	High	c	High	c
Phenytoin	2.67×10^{-5}	High	2.52	High	c	High	c	High	c	High	c	High	c
Propranolol	2.75×10^{-5}	High	0.28	High	c	High	c	High	c	High	c	High	c
Quinine	2.04×10^{-5}	High	0.54	High	c	High	c	High	c	High	c	High	c
Saquinavir	5.5×10^{-7}	Low	2.84	High	fp	Low	c	Low	c	High	fp	High	fp
Sulphasalazine	1.29×10^{-7}	Low	0.35	High	fp	Low	c	Low	c	High	fp	High	fp
Theophylline	4.47×10^{-5}	High	-0.18	High	c	High	c	Low	fn	Low	fn	Low	fn
Verapamil	2.63×10^{-5}	High	2.91	High	c	High	c	High	c	High	c	High	c
Zidovudine	6.93×10^{-6}	Low	-0.53	Low	c	High	fp	Low	c	Low	c	Low	c

¶ Calculated log *D* values at pH 6 using ACD/Labs; ** Taken from ref. 15; Ж taken from ref. 19;
Ref: reference; c: correct; fp: false positive; fn: false negative.

CONCLUSION

Within the limitations of our investigation, the following conclusions can be drawn. First, log $D_{6.0}$ showed better prediction capability than log *P*. Second, metoprolol was conservative permeability internal standard as compared to labetalol. Finally, models combining log *D* and PSA can have the best permeability prediction capabilities.

REFERENCES

1. Qiu Y, Chen Y, Liu L, Zhang G. Developing solid oral dosage forms: pharmaceutical theory and practice. USA, Elsevier Inc. 2009; 341-360.
2. Amidon GL, Lennernas H, Shah VP, Crison JR. A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. Pharm Res, 1995; 12: 413-420.
3. Cook J, Addicks W, Wu YH. Application of the biopharmaceutical classification system in clinical drug development--an industrial view. AAPS J, 2008; 10: 306-310.
4. Polli JE. In vitro studies are sometimes better than conventional human pharmacokinetic in vivo studies in assessing bioequivalence of immediate-release solid oral dosage forms. AAPS J, 2008; 10: 289-299.
5. Kasim NA, Whitehouse M, Ramachandran C, Bermejo M, Lennernas H, Hussain AS, Junginger HE, Stavchansky SA, Midha KK, Shah VP, Amidon GL. Molecular properties of WHO essential drugs and provisional biopharmaceutical classification. Mol Pharm, 2004; 1: 85-96.
6. Palm K, Stenberg P, Luthman K, Artursson P. Polar molecular surface properties predict the intestinal absorption of drugs in humans. Pharm Res, 1997; 14: 568-571.
7. World Health Organization (WHO). National Essential Medicines List of Pakistan, 2007 (4th Revision) at

http://apps.who.int/medicinedocs/fr/m/abstract/Js17119e/ accessed on 14/12/2010.
8. The European Agency for the Evaluation of Medicinal Products (EMA), Committee for Proprietary Medicinal Products (CPMP). Note for Guidance on the Investigation of Bioavailability and Bioequivalence. 2010.
9. Yalkowsky S, He Y. Handbook of aqueous solubility data. Boca Raton, FL. CRC Press. 2003.
10. Drugbank database. http://www.drugbank.ca/ accessed on 14/12/2010.
11. Syracuse Research Corporation. Physical/Chemical Property Database (PHYSPROP). SRC Environmental Science Center. Syracuse, NY. 1994.
12. Block J, Beale J. Wilson & Gisvold's Textbook of Organic Medicinal and Pharmaceutical Chemistry. MD. Lippincott Williams and Wilkins. 2004. 948-956.
13. Lindenberg M, Kopp S, Dressman JB. Classification of orally administered drugs on the World Health Organization Model list of Essential Medicines according to the biopharmaceutics classification system. Eur J Pharm Biopharm, 2004; 58: 265-278.
14. Kasim NA, Whitehouse M, Ramachandran C, Bermejo M, Lennernas H, Hussain AS, Junginger HE, Stavchansky SA, Midha KK, Shah VP, Amidon GL. Molecular properties of WHO essential drugs and provisional biopharmaceutical classification. Mol Pharm, 2004; 1: 85-96.
15. Rinaki E, Valsami G, Macheras P. Quantitative biopharmaceutics classification system: the central role of dose/solubility ratio. Pharm Res, 2003; 20: 1917-1925.
16. World Health Organization (WHO). Proposal to waive in vivo http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf.)
17. Kelder J, Grootenhuis PD, Bayada DM, Delbressine LP, Ploemen JP. Polar molecular surface as a dominating determinant for oral absorption and brain penetration of drugs. Pharm Res, 1999; 16: 1514-1519.
18. Food and Drug Administration (FDA), CDER. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER). Guidance for Industry: Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System. Food and Drug Administration, Ed. Rockville, MD. 2000.
19. Valope D. Drug Permeability Studies in Regulatory Biowaiver Applications. In: Ehrhardt C, Kim K, ed. Drug absorption studies: in situ, in vitro and in silico models. Springer NY 2008; 665-696.
20. Linnankoski J, Makela JM, Ranta VP, Urtti A, Yliperttula M. Computational prediction of oral drug absorption based on absorption rate constants in humans. J Med Chem, 2006; 49: 3674-3681.
21. Palm K, Luthman K, Ungell AL, Strandlund G, Beigi F, Lundahl P, Artursson P. Evaluation of dynamic polar molecular surface area as predictor of drug absorption: comparison with other computational and experimental predictors. J Med Chem, 1998; 41: 5382-5392.
22. Winiwarter S, Bonham NM, Ax F, Hallberg A, Lennernas H, Karlen A. Correlation of human jejunal permeability (in vivo) of drugs with experimentally and theoretically derived parameters. A multivariate data analysis approach. J Med Chem, 1998; 41: 4939-4949.
23. Box KJ. Comer JE. Using measured pKa, LogP and solubility to investigate supersaturation and predict BCS class. Curr Drug Metab, 2008; 9: 869-878.
24. Benet LZ, Larregieu CA. The FDA should eliminate the ambiguities in the current BCS biowaiver guidance and make public the drugs for which BCS biowaivers have been granted. Clin Pharmacol Ther, 2010; 88: 405-407.
25. Transporter Database, TP-Search. http://www.tp-search.jp/ accessed on 14/12/2010.